

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
12 December 2002 (12.12.2002)

PCT

(10) International Publication Number  
**WO 02/098286 A3**

- (51) International Patent Classification<sup>7</sup>: A01N 37/18, 43/04, A61K 31/70, 38/00 (74) Agent: WHITE, John, P.; Cooper & Dunahm LLP, 1185 Avenue of the Americas, New York, NY 10036 (US).
- (21) International Application Number: PCT/US02/18249 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 6 June 2002 (06.06.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 09/875,388 6 June 2001 (06.06.2001) US (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicants: THE TRUSTEES OF COLUMBIA UNIVERSITY IN CITY OF NEW YORK [US/US]; West 116th Street and Broadway, New York, NY 10027 (US). THE RESEARCH FOUNDATION OF STATE UNIVERISTY OF NEW YORK [US/US]; Office of Technology Licensing and Industry Relati, ons, N5002 Melville Library, Stony Brook, NY 11794-3369 (US). Published:  
— with international search report
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8 May 2003
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMPLANTATION OF BIOLOGICAL PACEMAKER THAT IS MOLECULARLY DETERMINED

(57) Abstract: This invention provides for a method of inducing a current in the heart in a subject which comprises contacting a cell of the heart of a subject with a compound in a sufficient amount to induce a current in the cell of the heart of a subject. This invention also provides a method of treating a cardiac condition in a subject which comprises contacting a cell of the heart of the subject with a compound in an amount sufficient to increase the current expression of the cell, thereby treating the cardiac condition in the subject.



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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/18249

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A01N 37/18, 43/04; A61K 31/70, 38/00

US CL : 514/2, 44

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 44

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	US 2002/0155101 A1 (DONAHUE et al) 24 October 2002 (24.10.2002), see pages 15-16.	1-6, 17-24
X, P	NATTEL et al. Arrhythmogenic ionic remodeling-Adaptive responses with maladaptive consequences Trends in Cardiovascular Medicine, October 2001, Vol. 11, No. 7, pp. 295-301, see entire document.	1-6, 17-24
Y, P		8-16
Y	US 6,231,518 B1 (GRABEK et al) 15 May 2001 (15.05.2001), see whole document.	1-24
X	WO 00/63434 A1 (UNIVERSITY OF UTAH RESEARCH FOUNDATION) 26 October 2000 (26.10.2000), see whole document, especially abstract, pages 43-48, 52-55.	1-8, 17-24
Y		9-16
A	RUBANYI, GABOR The future of human gene therapy Molecular Aspects of Medicine. 2001, Vol. 22, pages 113-142.	1-24

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

06 November 2002 (06.11.2002)

Date of mailing of the international search report

11 FEB 2003

Name and mailing address of the ISA/US

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Form PCT/ISA/210 (second sheet) (July 1998)

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/18249

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.  
☒ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

PCT/US02/18249

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-7, 17-24, drawn to a method of treating a cardiac condition in a subject which comprises contacting a cell of the heart of the subject with a compound in an amount sufficient to increase the current expression of the cell, thereby treating the cardiac condition in the subject. Species a), wherein the step of contacting the cell is systemic administration of the compound will be search with this Group. However, the other species in the group will be searched with the appropriate additional search fees.

Group II, claim(s) 8, drawn to a method of treating a cardiac condition in a subject which comprises contacting a cell of the heart of the subject with a compound in an amount sufficient to increase the current expression of the cell, thereby treating the cardiac condition in the subject, wherein the compound comprises a nucleic acid which encodes MiRP1.

Group III, claim(s) 9-12, drawn to a method of treating a cardiac condition in a subject which comprises contacting a cell of the heart of the subject with a compound in an amount sufficient to increase the current expression of the cell, thereby treating the cardiac condition in the subject, wherein the compound comprises a nucleic acid which encodes HCN channel.

Group IV, claim(s) 13-16, drawn to a method of treating a cardiac condition in a subject which comprises contacting a cell of the heart of the subject with a compound in an amount sufficient to increase the current expression of the cell, thereby treating the cardiac condition in the subject, wherein the compound comprises a nucleic acid which encodes HCN channel and a HCN channel.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

- a) systemic administration;
- b) topical application;
- c) injection electroporation;
- d) liposome application;
- e) viral mediated contact;
- f) contacting the cell with the nucleic acid; and
- g) co-culturing the cell with the nucleic acid.

The claims are deemed to correspond to the species listed above in the following manner:

- Claim 1 and claims dependent therefrom correspond to species a).
- Claim 1 and claims dependent therefrom correspond to species b).
- Claim 1 and claims dependent therefrom correspond to species c).
- Claim 1 and claims dependent therefrom correspond to species d).
- Claim 1 and claims dependent therefrom correspond to species e).
- Claim 1 and claims dependent therefrom correspond to species f).
- Claim 1 and claims dependent therefrom correspond to species g).

The following claim(s) are generic: claim 1.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

## INTERNATIONAL SEARCH REPORT

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The technical feature linking groups I-IV appears to be that they all relate to increases the current expression of a cell in the heart by administering a compound to the cell of the heart.

However, SCHMID et al. teaches orally administering a compound (oriprenaline) to increase the current expression of cardiac cells in a patient.

Therefore, the technical feature linking the inventions of Groups I-IV does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of Group I is considered to be a method to increases the current expression of a cell in the heart by administering a compound to the cell of the heart.

The special technical feature of Group II is considered to be a gene therapy method to increases the current expression of a cell in the heart by administering a compound to the cell of the heart, wherein the compound is MiRP1.

The special technical feature of Group III is considered to be a gene therapy method to increases the current expression of a cell in the heart by administering a compound to the cell of the heart, wherein the compound is HCN channel.

The special technical feature of Group IV is considered to be a method to increases the current expression of a cell in the heart by administering a compound to the cell of the heart, wherein the compound comprises the nucleic acid which encode MiRP1 and HCN channel.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: (a) the routes of administration are different structurally and/or functionally with regard to their action.

Accordingly, Group I-IV and species a)-g) are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept.

### Continuation of B. FIELDS SEARCHED Item 3:

WEST 2.1, STN

search terms: therapy, treating, cardiac condition, HCN1, HCN2, HCN4, MiRP1, cardiac rhythm disorder, gene therapy, cell, contracting, stimulating, membrane potential, shortening time, heart rate, current



FIGURE 8C

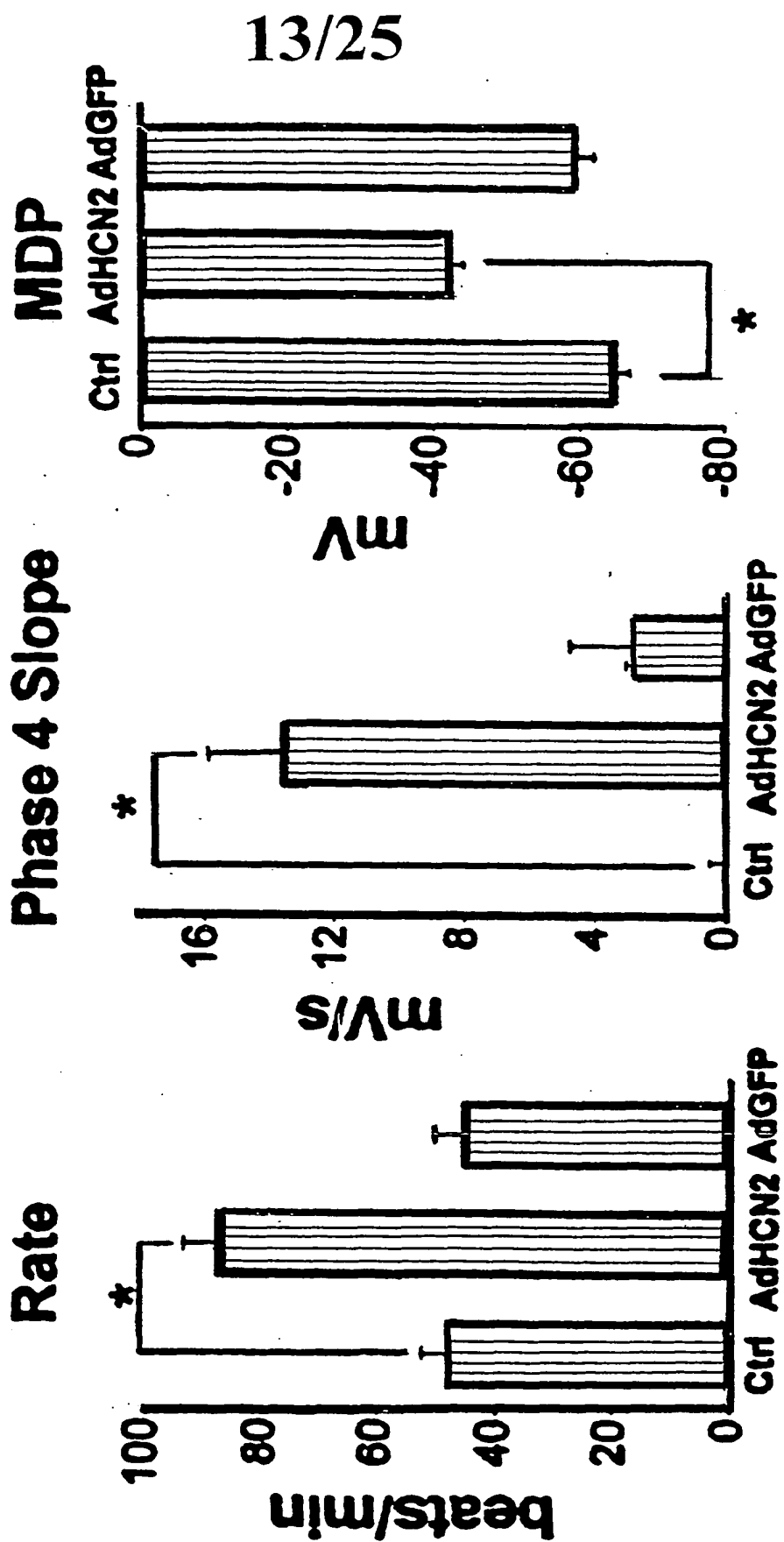
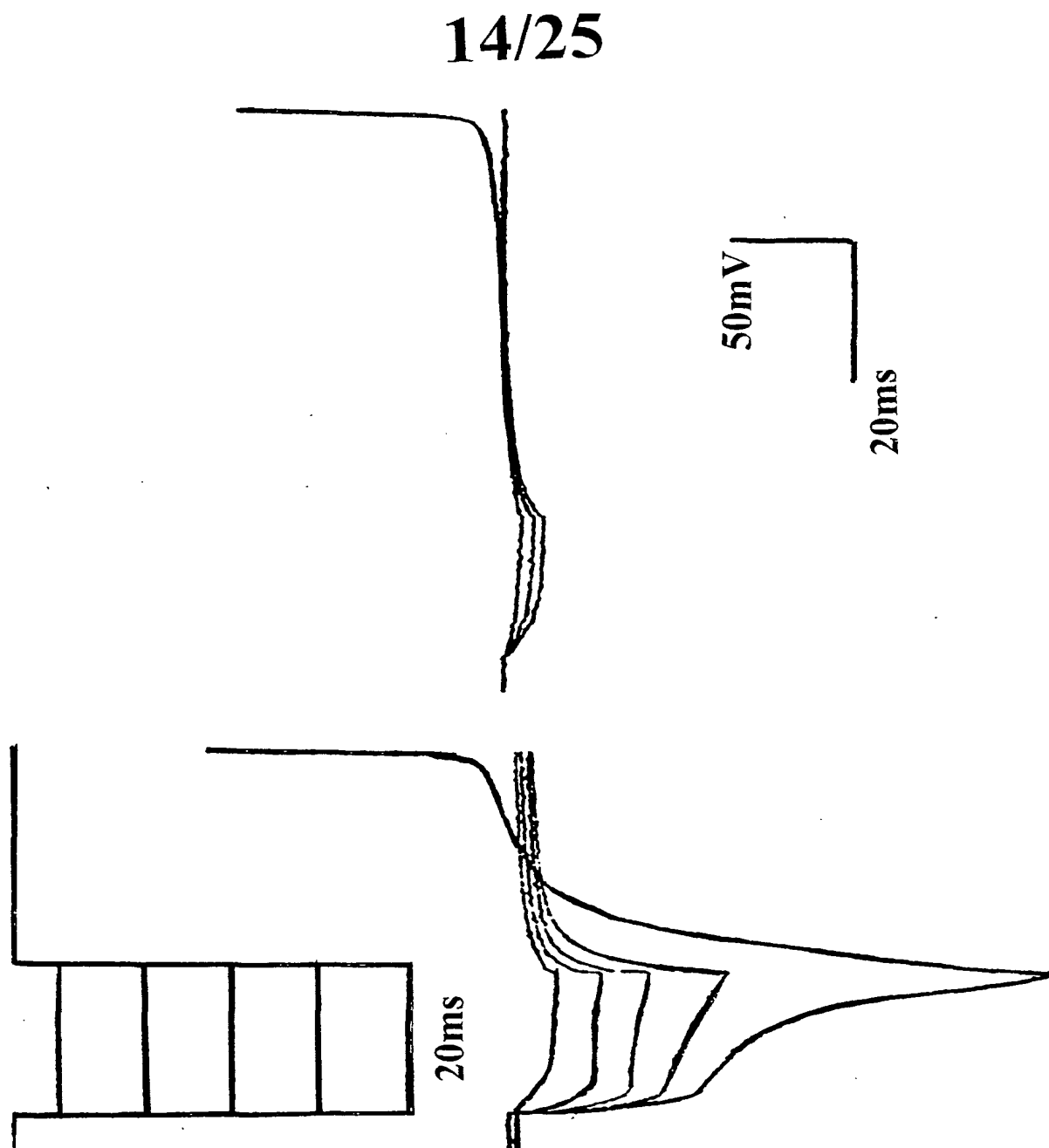


FIGURE 9A



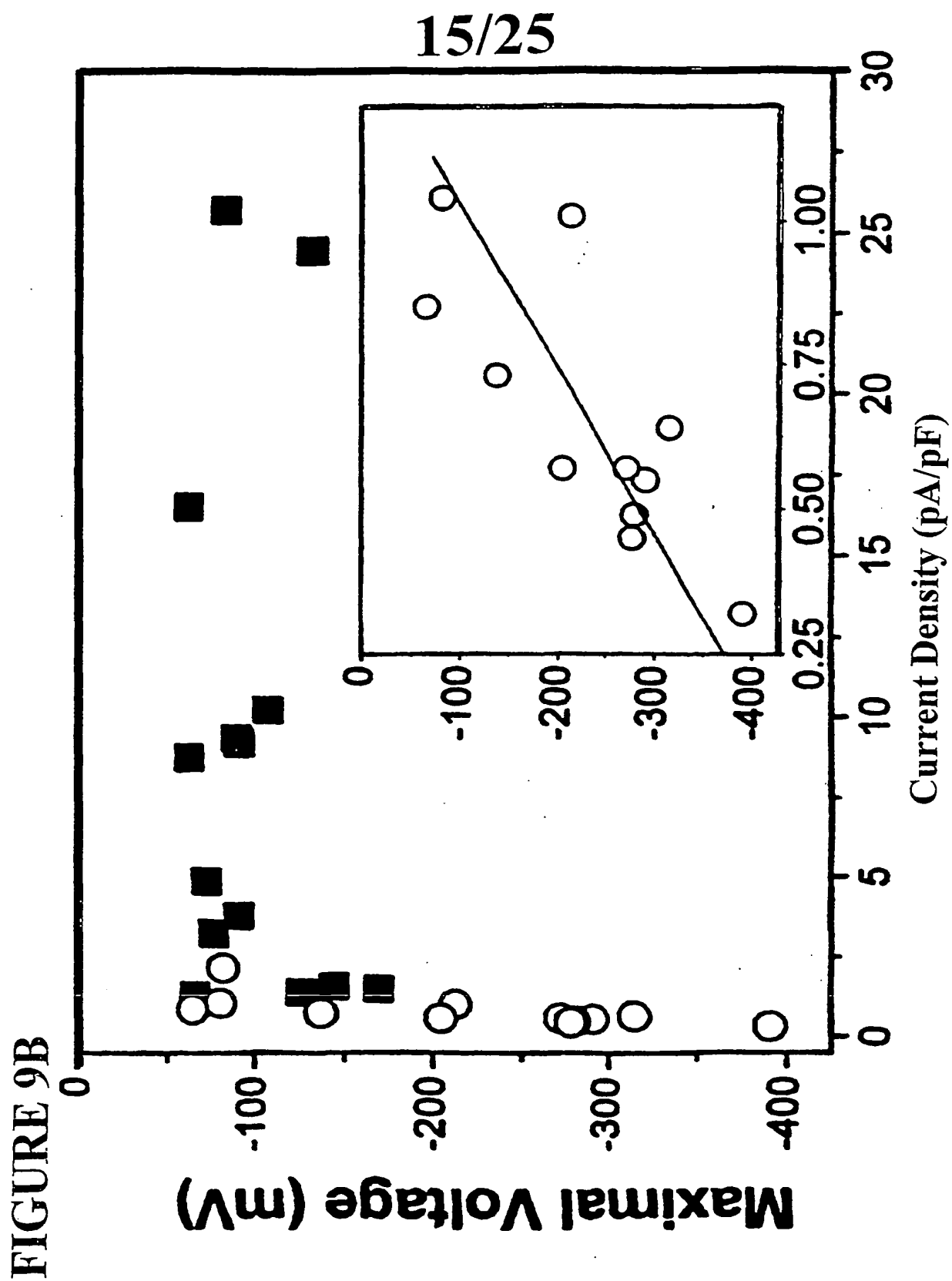


FIGURE 10A 16/25  
-- HCN1

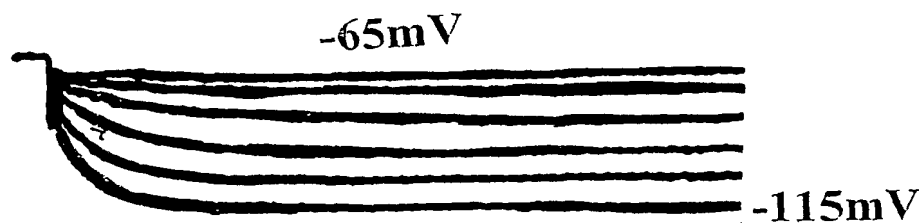


FIGURE 10B  
-- HCN1+minK

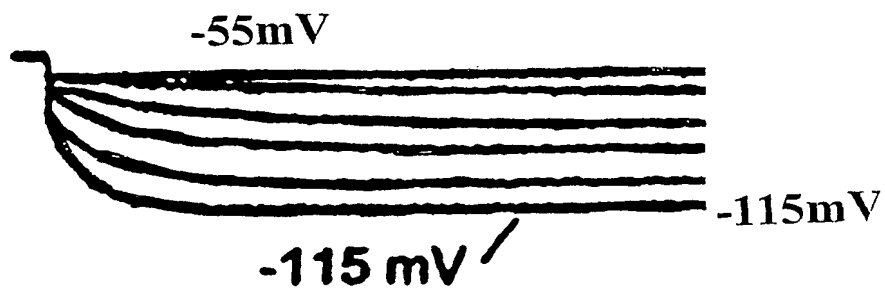
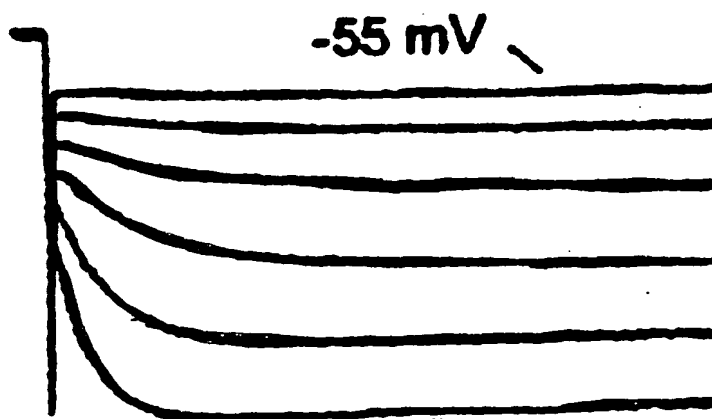


FIGURE 10C  
-- HCN1+MiRP1



-100nA

0.5sec

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FIGURE 10D

-- HCN2

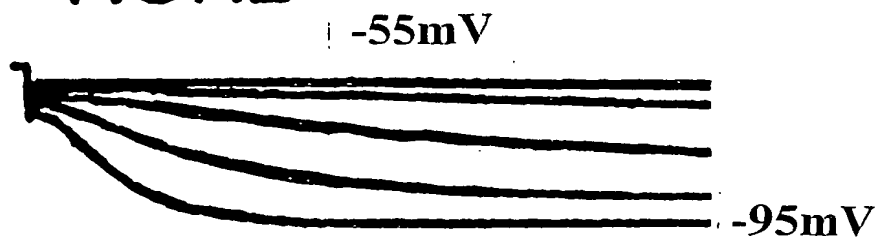
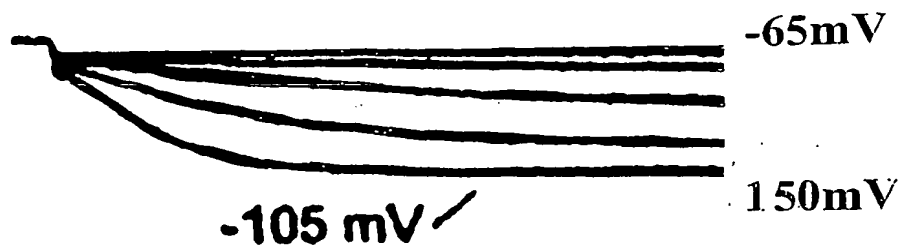


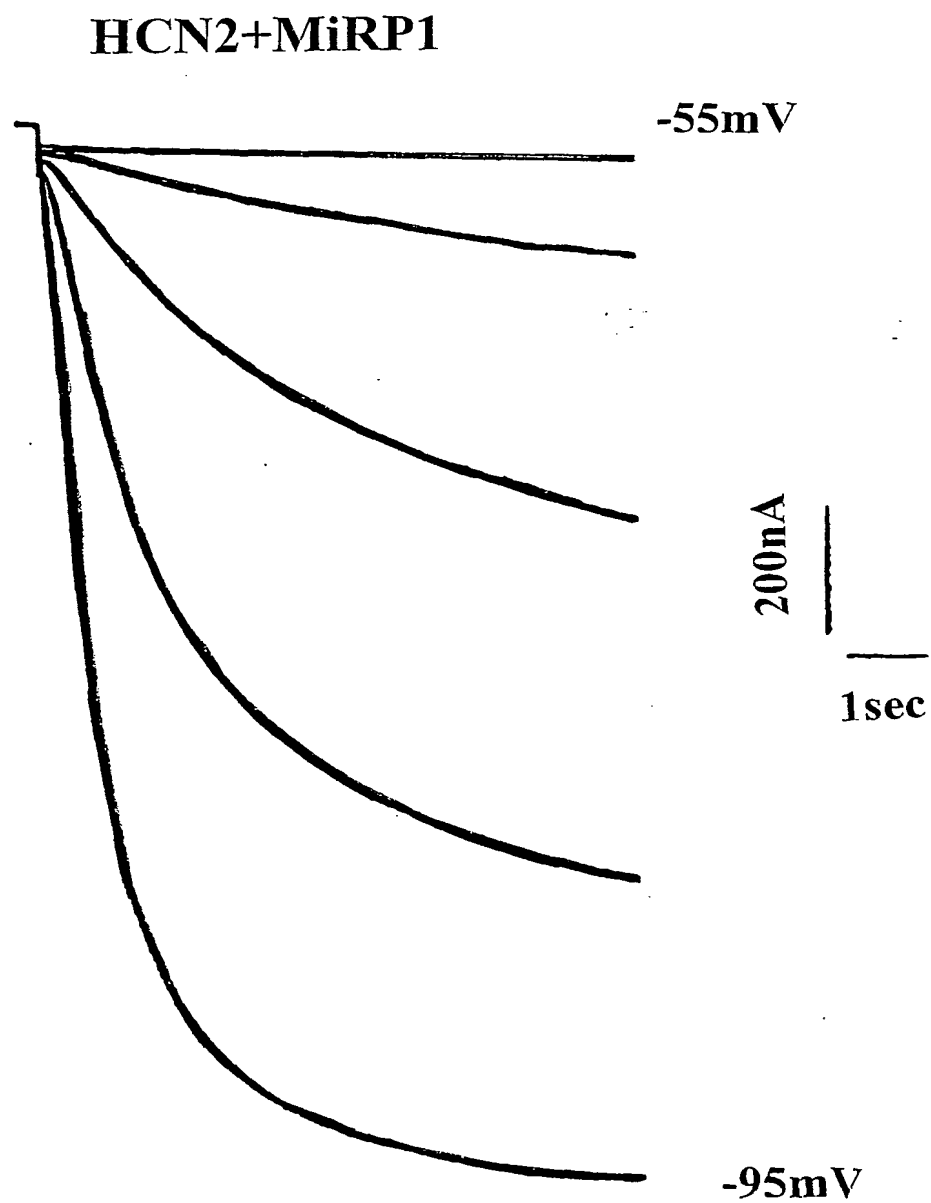
FIGURE 10E

-- HCN2 + minK



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FIGURE 10F



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FIGURE 10H

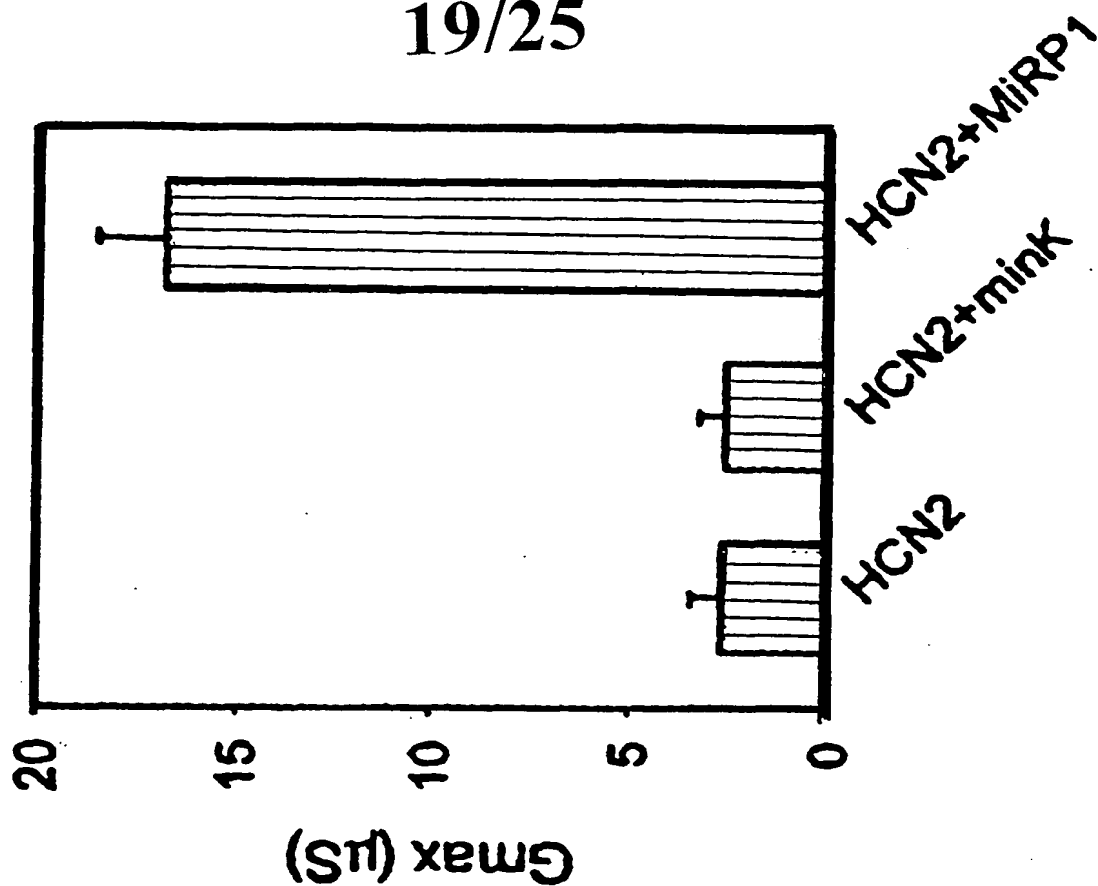


FIGURE 10G

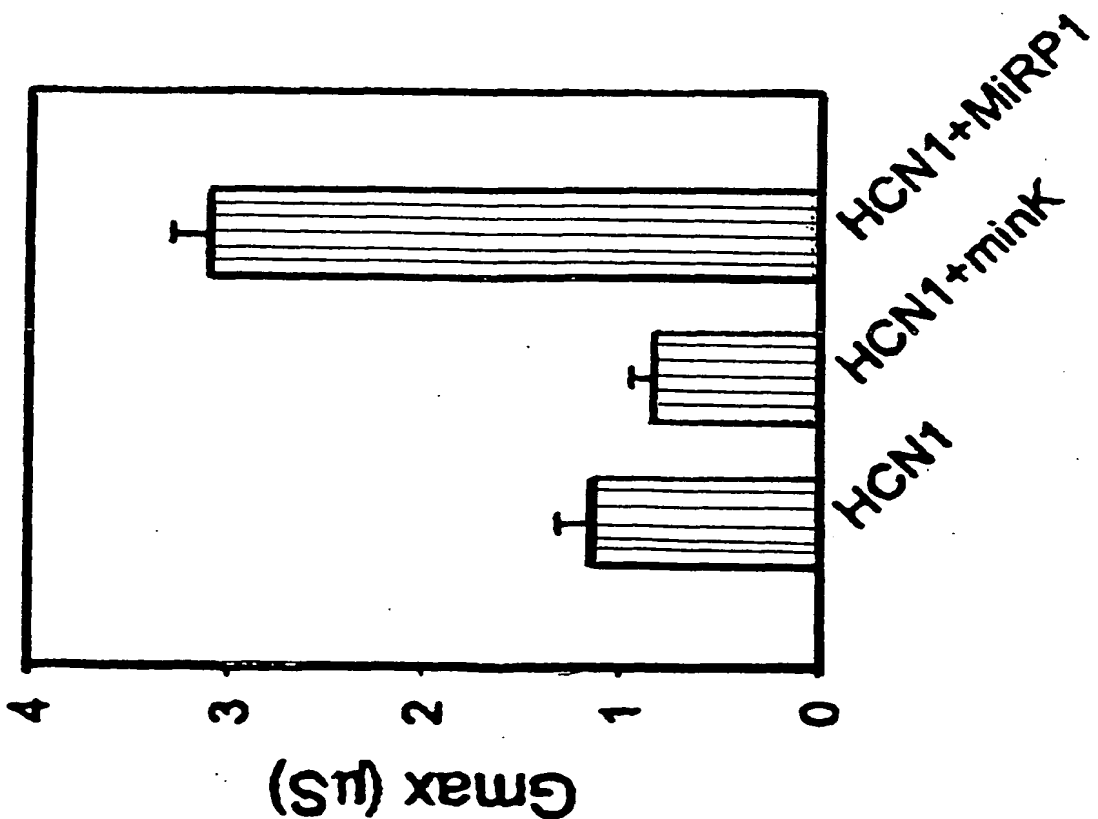


FIGURE 11B

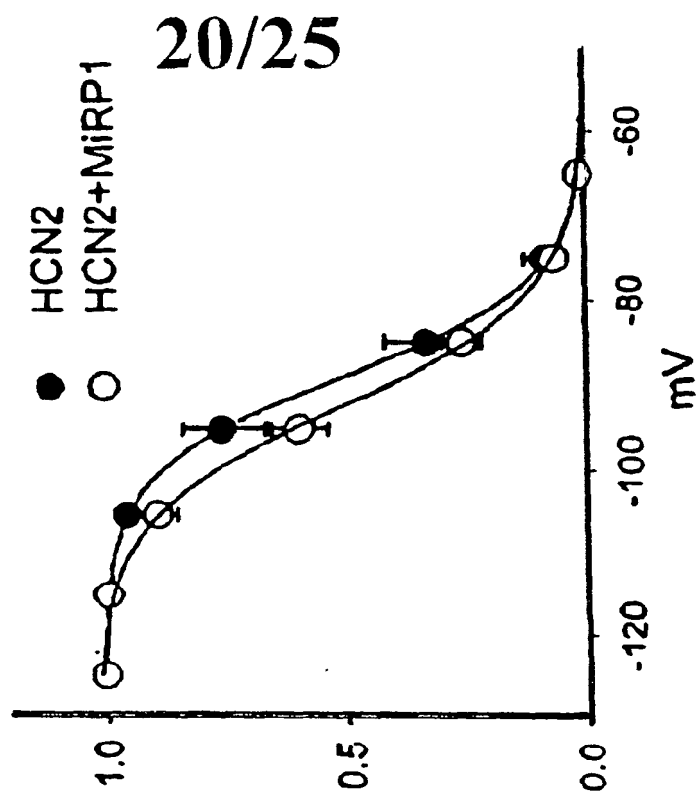
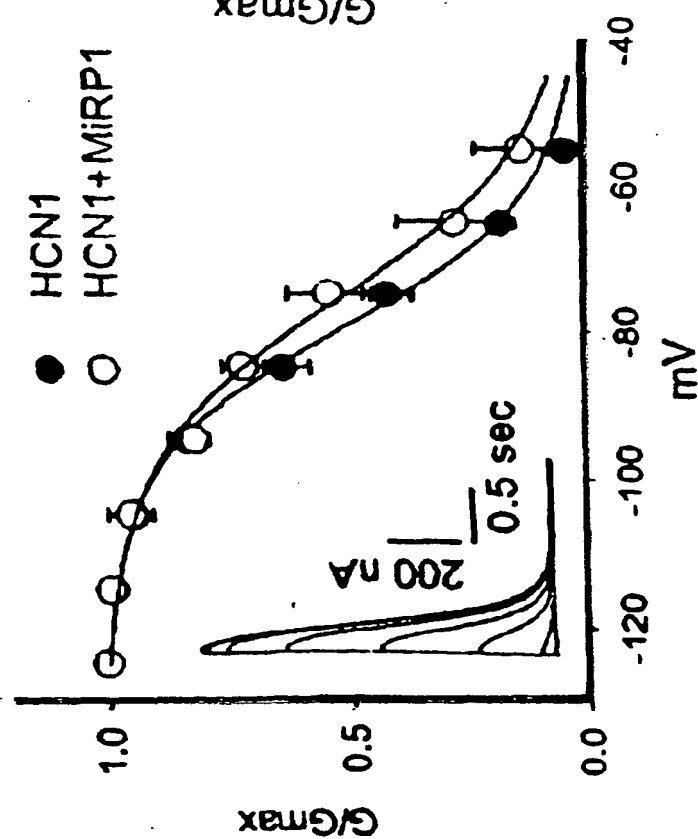


FIGURE 11A



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FIGURE 11D

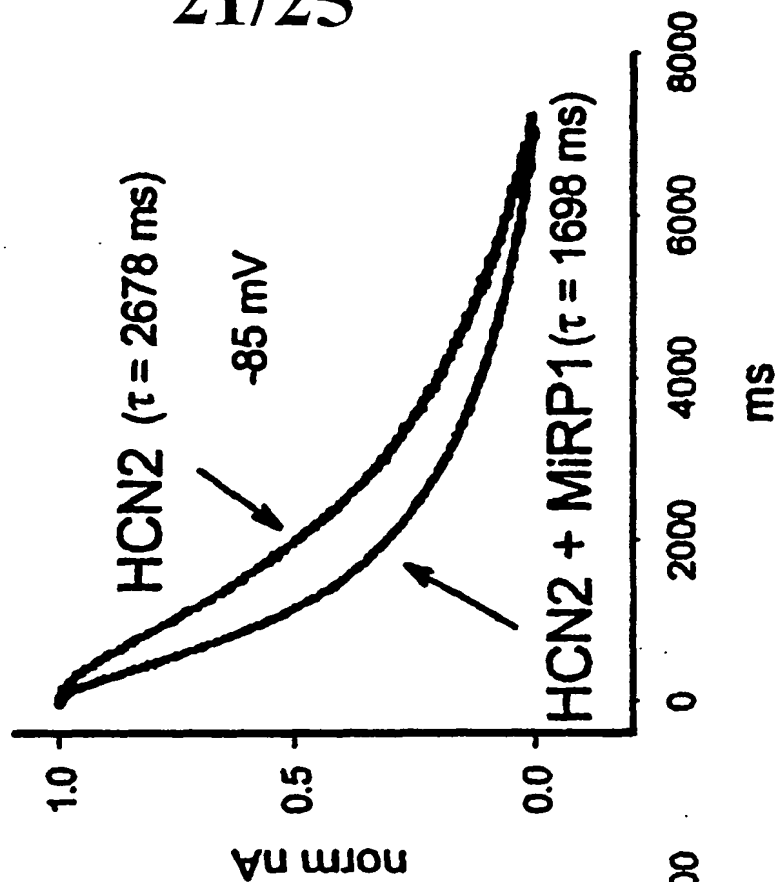
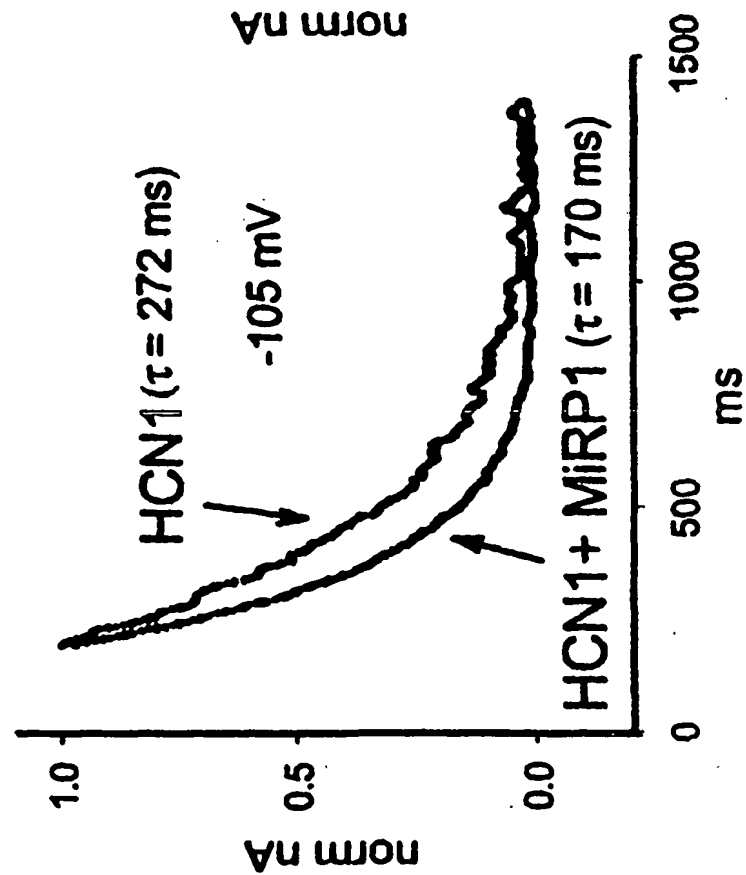


FIGURE 11C



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FIGURE 11F

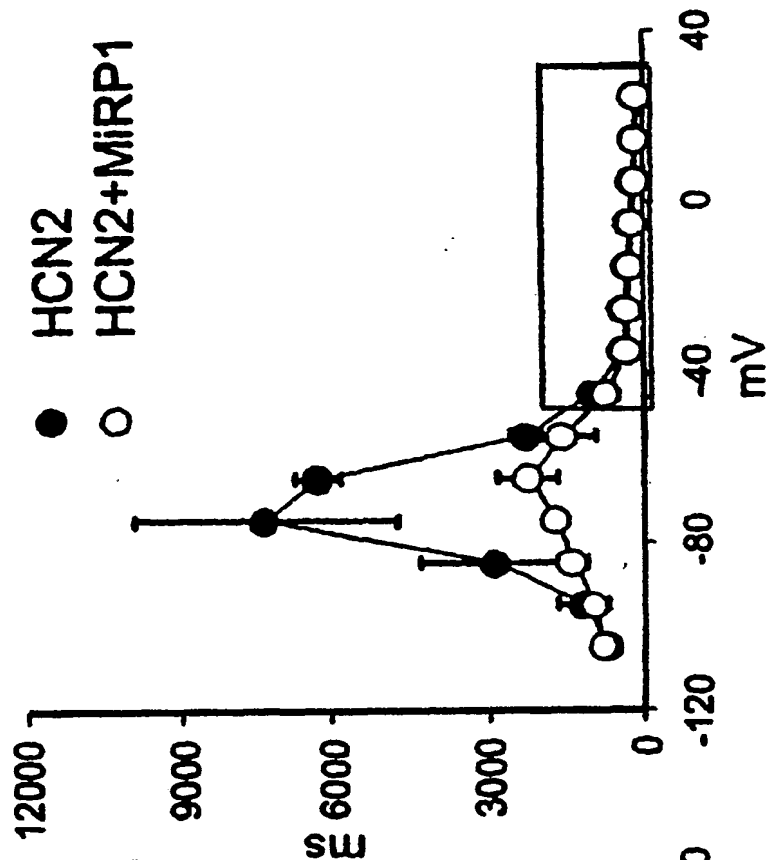
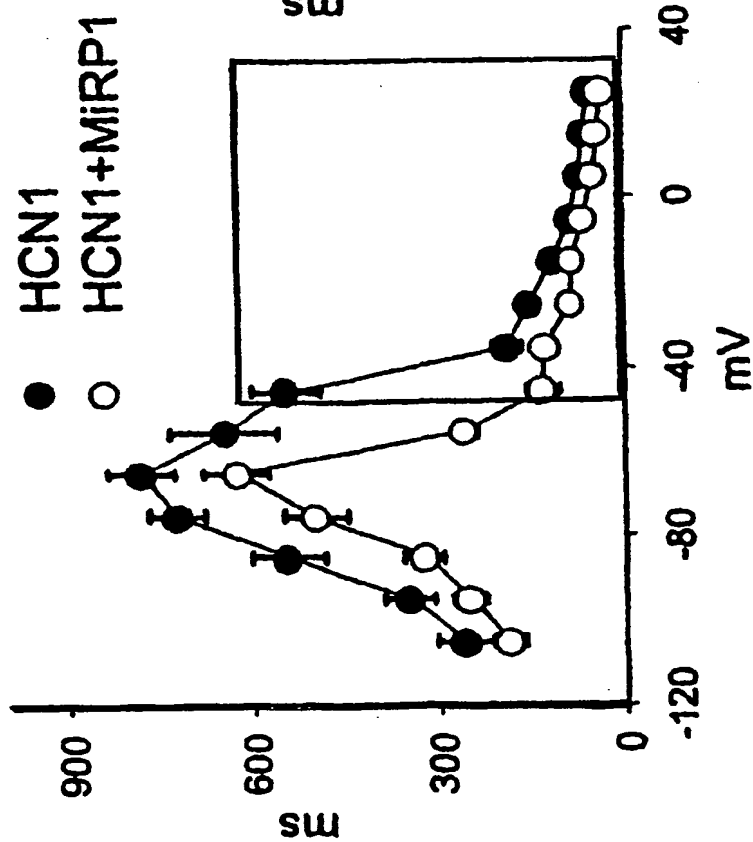
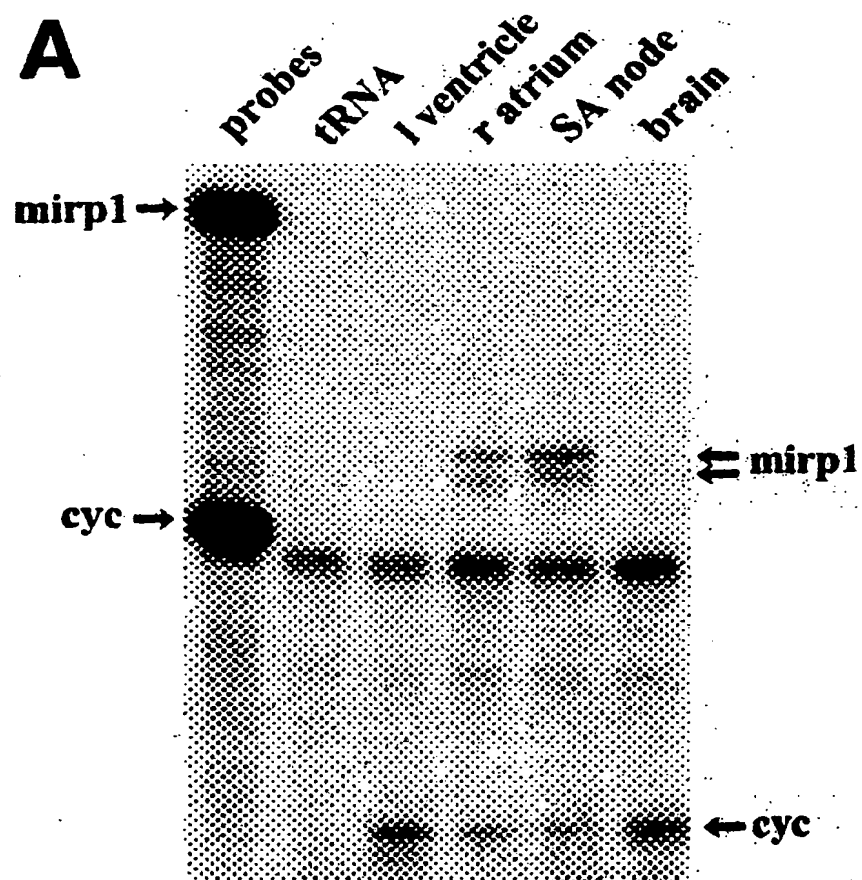


FIGURE 11E



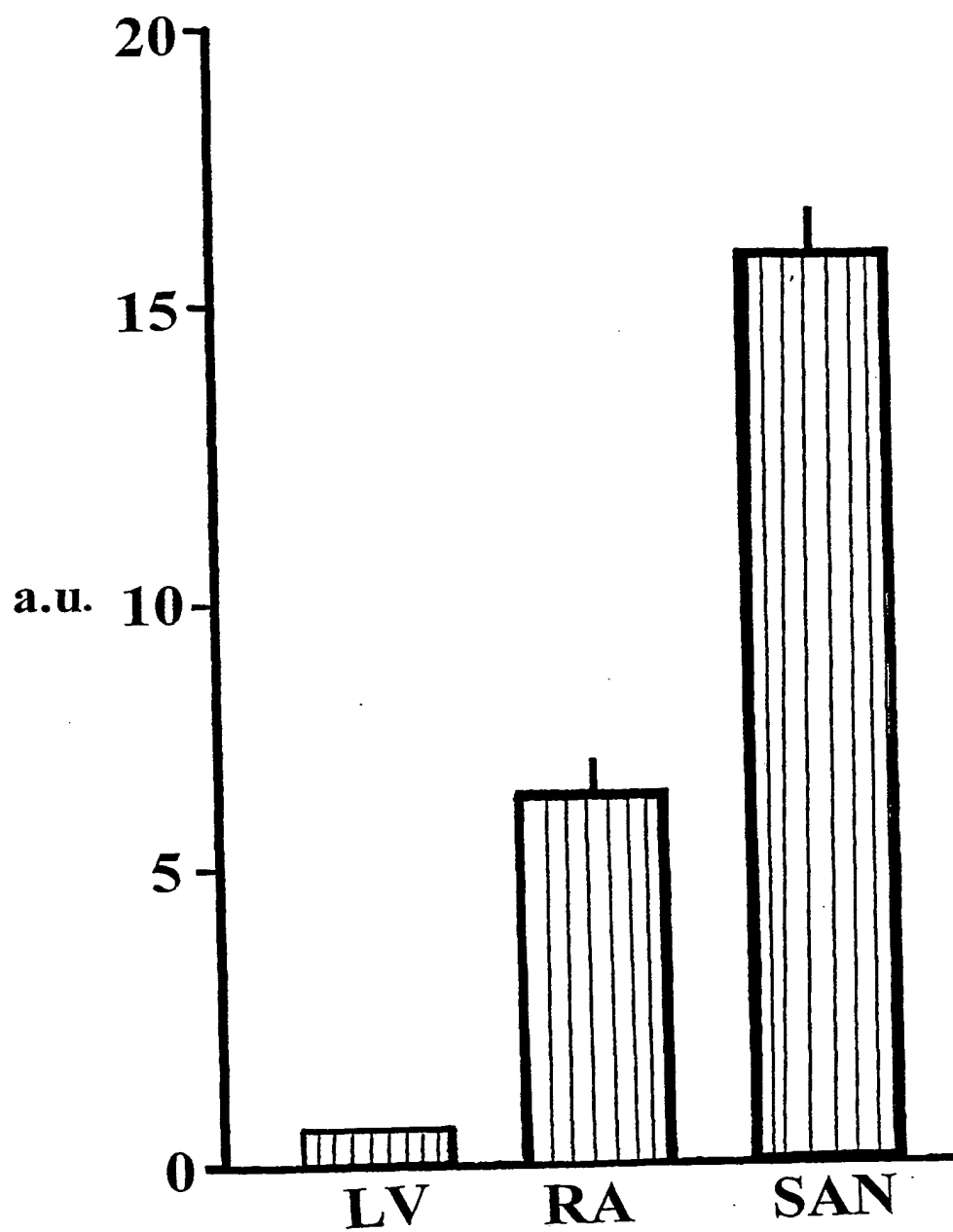
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FIGURE 12A



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FIGURE 12B



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FIGURE 13A

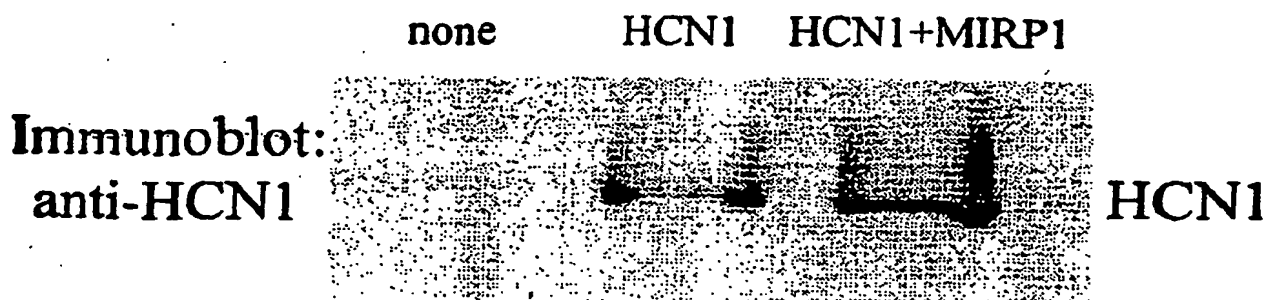


FIGURE 13B

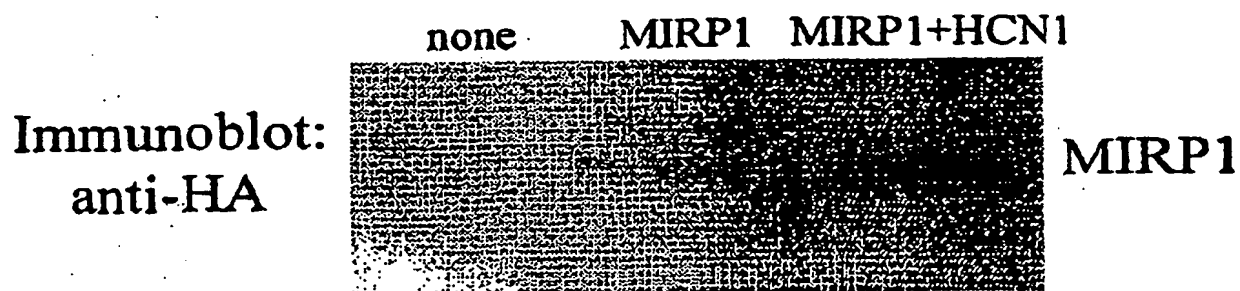
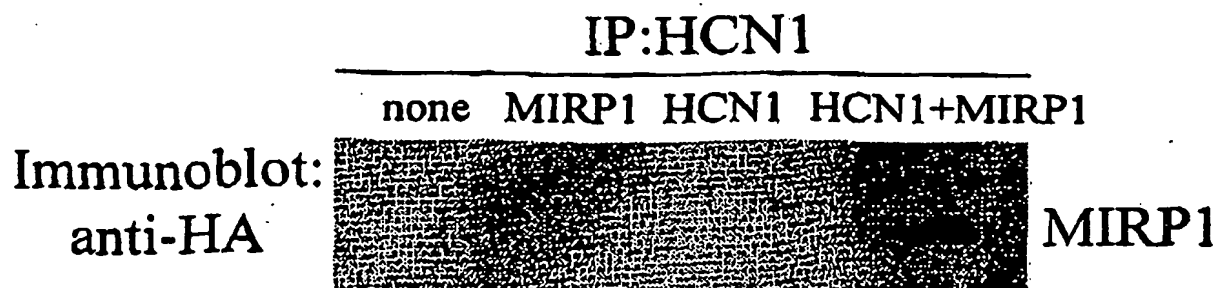


FIGURE 13C



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